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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,204	05/11/2001	Peter Martin Fischer	CCI-010CN	8487

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,204	FISCHER ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,49,51 and 53-75 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,49,51 and 53-75 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 49, 51 and 60 have been amended. Claims 50 and 52 have been amended. Claims 1, 49, 51 and 53-75 are pending and under consideration.

2. Text of sections of Title 35, U.S. Code not found in this action can be found in a previous action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 49, 51 and 53-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptides comprising SEQ ID NO:2, or the retro-inverted sequence of SEQ ID NO:2, does not reasonably provide enablement for peptides comprising variants comprising substitutions of spacer groups within SEQ ID NO:2, or variants comprising substitutions of two- basic resides of SEQ ID NO:2 with non-basic amino acids, or the reversal of less than all seven amino acids of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A) As drawn to peptides containing a "spacer group"

The instant invention is drawn to peptide having the ability to translocate through cell membranes, wherein said peptide is a variant of SEQ ID NO:1, or minimally comprises SEQ ID NO:2. Claim 1 is drawn to peptides having a "spacer group". or peptides having a spacer group in combination with other structural modifications. It is noted that the dependent claims are also included in this rejection because limitations which would be dependent on any of sections b, c, d, f or g would not exclude peptides having said limitations in combination with a spacer group according to section h of claim 1. The specification discloses preferred embodiments of "spacer group" on page 7, lines 10-12 as including multiple glycine residues or multiple beta-alanine residues, in addition to organic molecules of up to three carbons, "Suitable spacer groups that

may be inserted between any two amino acid residues of the carrier moiety include alkyl groups such as methyl, ethyl or propyl groups in addition to amino acid spacers such as glycine or p-alanine residues". The specification provides no limits as to the size of the spacer group which will separate amino acid residues of the disclosed core sequence of SEQ ID NO:2. It is logical to conclude that the configuration and charge of the peptide determines the ability of a peptide to translocate a cell membrane. Fischer et al (Journal of Peptide Research, 2000, Vol. 55, pp. 163-172, cited in a related application) teach that it is necessary for the translocating peptides to form an amphipathicity pattern which is duplicated by the retro-inverted sequences which also exhibit membrane translocating ability (page 170, first column, lines 7-12). It is noted that Fischer et al refer to this amphipaticity pattern as "whatever this may be". Thus, there are no teachings regarding the "breaking up" of the claimed sequences by spacer groups and the preservation of translocating ability because one of skill in the art has no indication of the characteristics of the amphipathicity pattern required for membrane translocation. The specification provides no teaching on the limitations of length or location of the "spacer group" that can be inserted between any of two amino acids in the disclosed peptides. The specification teaches a beta-alanine residue at a peptide terminus (page 26). The specification does not provide any example of multiple glycine or beta-alanine residues that can be inserted into the claimed peptides, in contrast to being attached to a terminus, without affecting the peptides translocating ability. One of skill in the art would be subjected to undue experimentation in order to make and use the broadly claimed peptides comprising a "spacer group".

(B) As drawn to peptides in which one or more amino acid residues of SEQ ID NO:2 are replaced by a naturally or non-naturally occurring amino acid residue.

Claim 1, part b is drawn to membrane translocation peptides in which one to three amino acid residues within SEQ ID NO:2 are substituted with naturally occurring or non-naturally occurring amino acids. It is noted that the dependent claims are also included in this rejection because limitations which would be dependent on any of sections c, d, e, f or g would not exclude peptides having said limitations in combination with the substituted peptide. The art teaches that each of the five C-terminal basic residues were particularly sensitive to substitution, when each residue was individually substituted with alanine. However, the substitution of a single alanine of the aforesaid basic positions, decreased but not eliminated peptide translocating

ability. However, the instant claims encompass the substitution of two amino acids within SEQ ID NO:2, and it is unclear how to make a peptide variant containing SEQ ID NO:2 wherein two amino acid substitutions have been made within SEQ ID NO:2. It is noted that Figure 3 of Fischer et al indicates that the substitution of a single alanine for the basic peptides at residues 30, 31, 33, 35 and 36 resulted in a peptide having much less than 50% of the translocating ability of wild-type penetratin. It would be reasonable to conclude that a second substitution of a basic amino acid residue within SEQ ID NO:2 would cause the loss of translocating ability. The specification does not qualify the particular residues which are tolerant of amino acid substitutions, or address the preservation of basic residues in order to preserve tithe amphipaticity pattern and the concomitant membrane translocating ability of the peptides. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed peptides.

(C) As drawn to peptides containing sequences in which the order of one or more amino acids is reversed..

Claim 1, section c is drawn to peptides in which the order of one or more amino acid residues of SEQ ID NO:2 are reversed. It is noted that the dependent claims are also included in this rejection because limitations which would be dependent on any of sections b, d, e, f or g would not exclude peptides having said limitations in combination with the limitation of section c. As stated above, the art teaches is necessary for the translocating peptides to form an amphipathicity pattern which is duplicated by the retro-inverted sequences which also exhibit membrane translocating ability (page 170, first column, lines 7-12). It is noted that Fischer et al refer to this amphipaticity pattern as "whatever this may be". Although the retro-inverted sequences would have the same amphipaticity pattern, the reversal of two amino acids within SEQ ID NO:2 would not guarantee the preservation of said amphipaticity pattern. Further, Fischer et al teach that each of the five C-terminal basic residues were particularly sensitive to substitution, when each residue was individually substituted with alanine. Fischer et al reported that this finding was in contrast with the substitution of the non-basic residues of the C-terminus of penetratin and attributed this affect to the substitution of a alanine as a neutral amino acid in place of a basic amino acid. The reversal of one or more amino acids would also read on the exchange of a basic amino acid within SEQ ID NO:2 with a non-basic amino acid and a

disruption of the amphipaticity pattern. The specification does not qualify the particular residues which are tolerant of amino acid substitutions, or address the preservation of basic residues in order to preserve tithe amphipaticity pattern and the concomitant membrane translocating ability of the peptides. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed peptides.

5. Claims 1, 49, 51 and 53-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 49 and 51 have been amended to recite the limitation" wherein one to three amino acid residues are replaced by a naturally occurring amino acid residue". the specification as filed states that one or more amino acids can be replaced by a naturally occurring or non-naturally occurring amino acid residue. The specification does not provide the limitation of substitution limited to three amino acids. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed invention at the time of filing. .

6. The rejection of claims 1, 51 and 60 under 35 U.S.C. 102(b) as being anticipated by Kalderon et al (Cell, 1984, Vol. 39, pp. 499-509) is withdrawn in light of applicants amendment which specifies replacement of one to three amino acids.

7. The rejection of claims 1 and 49-75 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,472,507 is maintained for reasons of record. It is noted that page 8 of the response indicates that the Terminal Disclaimer is being provided for US 6,472,507, said Paper was not received in the response.

8. The rejection of claims 1, 47, and 49-66 under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-9, 11-18 and 45 of

copending Application No. 09/438,460 is withdrawn in light of applicant's terminal disclaimer filed May 7, 2004.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella. Ph.D.
8/31/2004

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER